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*APPLICATION NUMBER:*  
**21-629**

**MEDICAL REVIEW**

# CLINICAL REVIEW COVER SHEET

<b>NDA number:</b>	<b>21-629</b>
<b>Review cycle:</b>	First
<b>Date/type of submission:</b>	June 18, 2003/Commercial
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<b>Sponsor:</b>	<b>Aventis Pharmaceuticals Inc., Bridgewater, NH 08807</b>
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<b>Division:</b>	<b>Metabolic and Endocrine Drug Products, HFD #: 510</b>
<b>Review completed:</b>	April 9, 2004
<b>Trade name:</b>	Apidra
<b>Generic name:</b>	<i>Insulin glulisine</i> (rDNA origin) injection (100 IU/mL)
<b>Code name:</b>	HMR1964
<b>Chemical name:</b>	3BLys-29BGlu-human insulin
<b>CAS registry number:</b>	207748-29-6
<b>Molecular formula:</b>	C <sub>258</sub> H <sub>384</sub> O <sub>78</sub> N <sub>64</sub> S <sub>6</sub>
<b>Molecular weight:</b>	5823
<b>Drug class:</b>	Short acting, soluble human insulin analogue
<b>Indication:</b>	Treatment of adults with Type 1 and Type 2 Diabetes mellitus
<b>Administration:</b>	Subcutaneous injection or pump infusion
<b>Therapeutic Category:</b>	<b>Metabolic Disorders</b> Diabetes, Diabetic Complications <i>Type-1 Diabetes (Insulin-Dependent, Juvenile-Onset)</i> <b>Metabolic Disorders</b> Diabetes, Diabetic Complications

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## EXECUTIVE SUMMARY

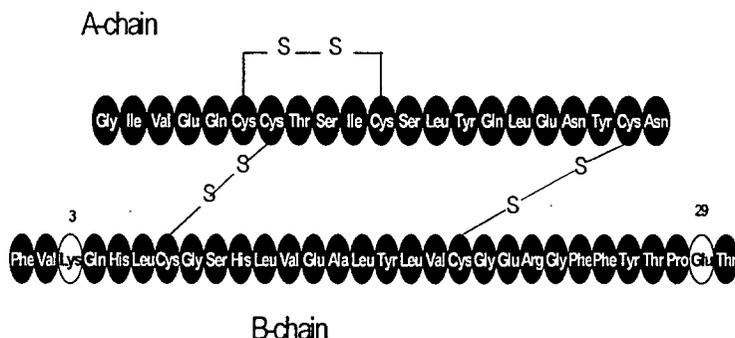
### I. Recommendations

- A. FROM THE CLINICAL PERSPECTIVE, APIDRA (*INSULIN GLULISINE*) MAY BE APPROVED FOR THE TREATMENT OF DIABETES MELLITUS.
- B. NO SPECIFIC RISK MANAGEMENT STEPS ARE RECOMMENDED. PHASE IV TRIALS IN CHILDREN WILL BE REQUIRED TO SUPPORT PEDIATRIC USE.

### II. Summary of Clinical Findings

#### A. OVERVIEW

This is the FDA clinical review of Apidra (*insulin glulisine*) NDA #21-629 submitted by Aventis Pharmaceuticals on June 18, 2003. *Insulin glulisine* is a new molecular entity (NME) being a novel insulin analog: 3<sup>B</sup>-lysine-29<sup>B</sup>-glutamic acid-human insulin. It is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. *Insulin glulisine* is proposed as a short acting, soluble human insulin analogue for the treatment of adults with Type 1 and Type 2 Diabetes mellitus. It will be administered by subcutaneous injection or via a subcutaneous pump infusion device. *Insulin glulisine* has the empirical formula  $C_{258}H_{384}N_{64}O_{78}S_6$  and its molecular weight is 5823.



As depicted, *insulin glulisine* differs from native human insulin by two amino acids at B3 and B29 positions, being lysine and glutamate instead of asparagine and lysine, respectively. Such modification of insulin structure is assumed to interfere with hexameric transformation of insulin molecules. Therefore they stay in the monomeric phase resulting in a faster onset and shorter duration of action. *Insulin glulisine* can therefore be administered 0-15 minutes before meals, as opposed to human regular insulin which is injected 30-45 minutes before meals in order to provide adequate glycemic control. The ability to administer insulin shortly before food ingestion is clinically desirable. It provides for a safety advantage because of reducing the risk of hypoglycemia related to failure to eat 30-45 minutes after insulin administration. It also has the therapeutic advantage of decreasing the potential of hyperglycemia related to missing an insulin dose. These potential advantages are expected without losing the therapeutic advantages of insulin therapy.

## B. EQUIPOTENCY WITH HUMAN INSULIN

In vitro trials indicated that the substitution of amino acids in the 3<sup>rd</sup> and 29<sup>th</sup> positions on the B chain of insulin does not decrease the binding of *insulin glulisine* to human insulin receptor. However, it appears to favor its signaling via insulin receptor substrate (IRS) Type 2 intracellular pathways. IRS-2 mediates the metabolic activities of insulin. The binding of insulin with IGF-1 receptors signals via a IRS-1 pathway to stimulate mitogenic activity. Findings in several animal and human muscle cells indicated that after binding to insulin receptor, signaling with *insulin glulisine* via IRS-1 is reduced, compared with human insulin, whereas its signaling via the IRS-2 pathway remains equipotent.

*Insulin glulisine* is clinically equipotent -in terms of glucose lowering activity- to regular human insulin as determined by steady state glucodynamics during the euglycemic clamp in healthy volunteers. In patients with Type 1 Diabetes, the overall glucose disposal induced by *insulin glulisine* administered immediately premeal, is equivalent to regular human insulin administered 30 min earlier. Clinical pharmacology trials indicated that after *insulin glulisine* administration, the onset of action is more rapid, and the time to maximum glucose excursion is shorter, than after regular human insulin. The absolute bioavailability of *insulin glulisine* after abdominal subcutaneous injections of 0.1 IU/kg is 73%. The time to peak concentrations ( $T_{max}$ ) of *insulin glulisine* is 51 min (82 min for regular human insulin), the volume of distribution in healthy subjects is 13L (21L for regular human insulin), the elimination half-life of *insulin glulisine* is 13 min (17 min for human insulin), and its clearance is 912 mL/min (1102 mL/min for human insulin).

## C. CLINICAL PRÉCIS

### I. The Clinical Development Program

#### 1. Overview

Five open-label, multinational, centrally randomized, active-controlled, parallel-group Phase III Clinical Trials comprised the clinical evidence component of *insulin glulisine* NDA and are the focus of this review. Due to the nature of diabetes and the availability of other treatments and as agreed upon with the Agency, none of the Phase III Trials was designed to prove superiority to a placebo control group. The goal of the Phase III Trials was to establish proof of noninferiority to other approved insulins. Three trials (3001, 3004 and 3006) were performed in Type 1 patients, and two (3002, 3005) were completed in Type 2 patients.

Three of these trials (3001, 3002 and 3005) had 26 weeks treatment periods, constituting the pivotal trials. Fifty three percent of the Phase III Trials subjects (participating in 3001 and 3002) continued to be followed up for a total of 52 weeks. These extension trials are referred to as 3011 and 3012, respectively. They support an evaluation of long-term safety (up to 1 year of exposure).

Two trials (3004 and 3006) lasted for 12-week. Trial 3004 was conducted to support a post mealtime administration dosing recommendation. It was conducted in patients with Type 1 Diabetes, comparing the efficacy and safety of 1) postmeal *insulin glulisine* to regular insulin, 2) postmeal *insulin glulisine* to premeal *insulin glulisine*, and 3) premeal *insulin glulisine* to regular insulin. Trial 3006, was designed to support the claim that *insulin glulisine* may be safely administered by continuous s.c. insulin infusion (CSII) via an external insulin pump to control hyperglycemia in patients with Type 1 Diabetes. It compared the safety and compatibility of *insulin glulisine* and Insulin aspart (Novolog) when used in external pumps, in terms of catheter occlusions, infusion site reactions, unexplained hyperglycemia, rate of catheter change, GHb,

insulin doses, BG parameters, hypoglycemic episodes, adverse events, laboratory data, and vital signs.

**Table 1: The number of subjects included in Phase III Clinical Trials (Phase III studies)**

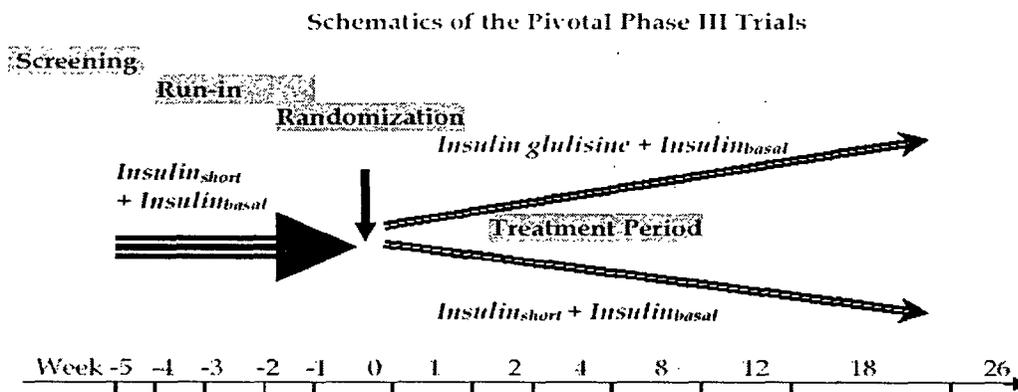
	No. studies	No. subjects treated		
		Total	Glulisine	Comparators
Subjects with type 1 diabetes	3 (+ 1 extension)	1591	950	641
Study 3001/3011	—	672	339	333
(Study 3011) <sup>a</sup>	—	(589)	(302)	(287)
Study 3004	—	860	582	278
Study 3006	—	59	29	30
Subjects with type 2 diabetes	2 (+ 1 extension)	1766	883	883
Study 3002/3012	—	876	435	441
(Study 3012) <sup>a</sup>	—	(709)	(357)	(352)
Study 3005	—	890	448	442
<b>Total exposed Phase III</b>	<b>5 (+ 2 extensions)</b>	<b>3357</b>	<b>1833</b>	<b>1524</b>

The protocol design of the three pivotal efficacy trials (3001, 3002 and 3005) was similar. Likewise were the inclusion/exclusion criteria, the target BG values (assessed by home BG monitoring), and the primary and secondary outcome variables.

**2. Phase III Clinical Trials**

The safety and efficacy of *insulin glulisine* were studied in adult patients with Type 1 and Type 2 Diabetes. The primary efficacy parameter was glycemic control, as measured by glycated hemoglobin (GHb), and expressed as hemoglobin A1c equivalents (A1C).

**Figure 1: An overview of the general design of the 3 pivotal Phase III Trials**



**3. Safety and Efficacy in Type 1 Diabetes**

**Clinical Trial 3001**

A 26-week, randomized, open-label, active-control trial (n = 672) was conducted in patients with Type 1 Diabetes to assess the safety and efficacy of *insulin glulisine* compared to insulin lispro (Homolog) when administered subcutaneously within 15 minutes before a meal. Insulin glargine was administered once daily in the evening as the basal insulin. Before start of the trial there was a 4-week run-in period combining insulin lispro (Homolog) and insulin glargine followed by randomization. Glycemic control and the rates of hypoglycemia requiring intervention from a third party, were comparable for the two treatment regimens. The number of daily short-acting insulin injections and the total daily doses of *insulin glulisine* and insulin lispro (Homolog) were similar.

**Table 2: Trial 3001 in adults with Type 1 Diabetes**

Treatment duration Treatment in combination with:	26 weeks Insulin glargine	
	<u>Insulin glulisine</u>	<u>Insulin lispro</u>
HbA1c (%)		
Number of patients	331	322
Baseline mean	7.60	7.58
Adj. mean change from baseline	-0.14	-0.14
APIDRA – Insulin Lispro		0.00
95% CI for treatment difference		(-0.09; 0.10)
Basal insulin dose (IU/day)		
End trial mean	24.16	26.43
Adj. mean change from baseline	0.12	1.82
Short-acting insulin dose (IU/day)		
End trial mean	29.03	30.12
Adj. mean change from baseline	-1.07	-0.81
Severe symptomatic hypoglycemia	4.8%	4.0%
Percent of patients (n/total N)	(16/335)	(13/326)

#### 4. Safety and Efficacy in Type 2 Diabetes Clinical Trials 3002 and 3005

Two 26-week, randomized, open-label, active-control trials (n = 876, 890) were conducted in insulin-treated patients with Type 2 Diabetes to assess the safety and efficacy of *insulin glulisine* given within 15 minutes before a meal compared to regular human insulin administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period combining regular human insulin and NPH human insulin. The average body mass index (BMI) of patients was above 30 kg/m<sup>2</sup> in both trials. At randomization, a proportion of the patients were on an oral hypoglycemic agent and were instructed to continue use of their oral hypoglycemic agent at the same dose. The majority of patients (78%) in trial 3002 mixed their short-acting insulin with NPH human insulin immediately prior to injection. A reduction from baseline A1C was seen in both arms of both trials. The rates of hypoglycemia, requiring intervention from a third party, were comparable for the two treatment regimens in both trials.

**Table 3: Trials 3002, 3005 in adults with Type 2 Diabetes**

Treatment duration Treatment in combination with:	26 weeks NPH human insulin	
	<u>Insulin glulisine</u> 3002, 3005	<u>Regular human insulin</u> 3002, 3005
Number of subjects treated	404, 448	403, 442
Hb A1C (%)		
Baseline mean	7.57, 7.58	7.50, 7.50
Adj. mean change from baseline	-0.46, -0.32	-0.30, -0.35
<i>insulin glulisine</i> – Regular Human Insulin	-0.16, 0.03	
95% CI for treatment difference		(-0.26; -0.05), (-0.07; 0.13)
Basal insulin dose (IU/day)		
End trial mean	65.34, 47.09	63.05, 45.94
Adj. mean change from baseline	5.73, 4.54	6.03, 4.81
Short-acting insulin dose (IU/day)		
End trial mean	35.99, 34.01	36.16, 35.58
Adj. mean change from baseline	3.69, 2.95	5.00, 4.47

Severe symptomatic hypoglycemia Percent of patients	1.4, 1.3	1.2, 3.2
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5. **Timing of Administration: Pre- and Post-Meal**

**Clinical Trial 3004 in Type 1 Diabetes** was a 12-week, randomized, open-label, active-control trial (n = 860) to assess the safety and efficacy of *insulin glulisine* administered at different times with respect to a meal. *Insulin glulisine* was administered subcutaneously either within 15 minutes before a meal or immediately after a meal and regular human insulin was administered subcutaneously 30 to 45 minutes prior to a meal. The comparisons performed in this trial were premeal *insulin glulisine* compared to regular human insulin, postmeal *insulin glulisine* compared to regular human insulin, and postmeal *insulin glulisine* compared to premeal *insulin glulisine*. Insulin glargine® was administered once daily at bedtime as the basal insulin. Before start of the trial there was a 4-week run-in period combining regular human insulin and insulin glargine followed by randomization. Glycemic control and the rates of hypoglycemia requiring intervention from a third party were comparable for the treatment regimens. Significant reductions from baseline in A1C were observed in all three treatment regimens. No changes from baseline between the treatments were seen in the total daily number of short-acting insulin injections.

Table 4: Trial 3004 evaluating postmeal administration of *insulin glulisine* in adults with Type 1 Diabetes

Treatment duration	12 weeks	12 weeks	12 weeks
Treatment in combination with:	Insulin glargine	Insulin glargine	Insulin glargine
	<u><i>Insulin glulisine</i></u>	<u><i>Insulin glulisine</i></u>	<u>Regular human</u>
	<u>post meal</u>	<u>pre meal</u>	<u>insulin</u>
HbA1c			
Number of patients	276	268	257
Baseline mean	7.70	7.73	7.64
Adj. mean change from baseline*	-0.11	-0.26	-0.13
Basal insulin dose (IU/day)			
End trial mean	28.77	29.49	28.46
Adj. mean change from baseline	0.24	0.99	0.65
Short-acting insulin dose (IU/day)			
End trial mean	28.06	28.44	29.23
Adj. mean change from baseline	-0.47	-0.88	1.75
Severe symptomatic hypoglycemia	8.4%	8.4%	10.1%
Percent of patients (n/total N)	(25/296)	(24/286)	(28/278)

\*Adj. mean change from baseline treatment difference (98.33% CI for treatment difference): *Insulin glulisine* pre meal vs. regular human insulin - 0.13 (-0.26; 0.01); *Insulin glulisine* post meal vs. Regular Human Insulin 0.02 (-0.11; 0.16); *Insulin glulisine* post meal vs. pre meal 0.15 (0.02; 0.29).

6. **Delivery of *Insulin glulisine* via Continuous Subcutaneous Insulin Infusion (CSII)**

**Clinical Trial 3006 in Type 1 Diabetes** evaluated the use of *insulin glulisine* for administration using an external pump in comparison to insulin aspart (Novolog). The trial was a 12-week randomized, open-label, active-control and included 59 patients with Type 1 Diabetes. A low monthly rate of catheter occlusion in both treatment groups was observed. The incidence of infusion site reactions seen with *insulin glulisine* was comparable to insulin aspart.

Table 5: Trial 3006 evaluating the administration of *insulin glulisine* via CSII (pump) devices

	<u><i>Insulin glulisine</i></u>	<u>Insulin aspart</u>

Catheter occlusions/month	0.08	0.15
Infusion site reactions	10.3% (3/29)	13.3% (4/30)

## II. Valid Claims

From the clinical perspective, this author finds the following claims valid based on the statistically significant data presented in NDA # 21,629.

### 1. Efficacy

In patients with Type 1 Diabetes using insulin glargine as the basal insulin, *insulin glulisine* was noninferior to insulin lispro (Homolog) in GHb change from baseline to endpoint. For both treatment groups, the mean GHb reduction was 0.14% from a baseline of 7.6%. The upper limit of the 2-sided 95% confidence interval for treatment difference (0%) was 0.1% which is less than the prespecified 0.4% noninferiority margin. In patients with Type 2 Diabetes using NPH as the basal insulin with or without OHA, *insulin glulisine* was noninferior to regular insulin in GHb change from baseline to endpoint. Mean GHb changes for glulisine and regular insulin were -0.46% and -0.30% (Trial 3002) and -0.32% and -0.35% (Trial 3005), respectively. The upper limits of the 2-sided 95% confidence intervals, -0.05% and +0.13%, for the treatment differences of -0.16% and +0.03% for the 2 trials were within the 0.4% noninferiority margin. The 12-week trial on timing of glulisine administration compared postmeal, premeal, and regular insulin. The GHb changes from baseline were -0.11%, -0.26%, and -0.13% for the 3 treatment groups, respectively. The upper limits of the 98.33% confidence intervals were all within the noninferiority margin of 0.4%: -0.02% for the -0.15% difference between premeal and postmeal, 0.01% for the -0.13% difference between premeal glulisine and regular insulin, 0.16% for the +0.02% difference between postmeal glulisine and regular insulin. Additionally, trial 3006 showed evidence in patients with Type 1 Diabetes that *insulin glulisine* administered via CSII is noninferior to insulin aspart (Novolog) in terms of GHb reduction, injection site reactions and catheter occlusions.

### 2. Dosing and administration

*Insulin glulisine* is administered by subcutaneous injection as the short acting insulin to control postprandial glucose levels in diabetic patients receiving appropriate dosage of a basal (longer acting) insulin. The dosage of *insulin glulisine* should be individualized and determined based on the physician's advice in accordance with the needs of the patient. *Insulin glulisine* is administered 0-15 minutes before the meals. Delaying the injection of *Insulin glulisine* for up to 20 minutes after starting the meal does not significantly reduce its safety or efficacy. If it is necessary to mix *insulin glulisine* with NPH insulin to minimize the number of injections, *insulin glulisine* should be drawn into the syringe first. Injection should be made immediately after mixing. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables, requiring closer monitoring of blood glucose. *Insulin glulisine* should be administered by subcutaneous injection in the abdominal wall, the thigh or the deltoid. As with all insulins, injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The site of SC administration does not play an important role in the PK or PD of *insulin glulisine*. *Insulin glulisine* can also be administered via a continuous subcutaneous insulin infusion (CSII) system (insulin pump).

### 3. Safety

*Insulin glulisine* treatment does not seem to elicit any safety signals other than those known to be associated with insulin treatment. The overall adverse events profile associated with *insulin glulisine* treatment is equivalent to the adverse events profile associated with human regular insulin in patients with Type 2 Diabetes. The overall adverse events profile associated with *insulin glulisine* treatment is equivalent to the adverse events profile associated with insulin lispro (Homolog) in patients with Type 1 Diabetes. In diabetic patients receiving their insulin via a SCII system (insulin pump), the pump specific adverse events (e.g. occlusion) associated with *insulin glulisine* treatment are roughly equivalent to those associated with Insulin aspart (Novolog) treatment. No specific population appears to be more susceptible to the adverse events associated with *insulin glulisine* treatment.

4. **Special populations**

The effects of *insulin glulisine* do not appear to differ based on the patients' age, race, gender, or body weight. Caution must be exercised if *insulin glulisine* is to be administered to patients with renal insufficiency, hepatic impairment, pregnancy, or lactation. The safety and efficacy of *insulin glulisine* in children have not been established yet.

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## THE CLINICAL REVIEW

### I. Approach to Clinical Review

This review begins with an overview of the quality and adequacy of the submitted data in support of the sponsor's claims. I then address the sponsor's specific claims for dosing and administration, safety, and efficacy. My comments, focusing on the issues of particular significance, from the regulatory and clinical perspectives, will follow. In this review of a novel insulin-like molecule, these comments will summarize

1. Whether human trials support the specificity of *insulin glulisine's* actions to insulin receptors, i.e. whether *insulin glulisine* causes any adverse events in humans that are not known to be caused by insulins.
2. The relative clinical safety of *insulin glulisine* compared with other insulin products, particularly in terms of death, serious adverse events, and immunogenicity.
3. The degree to which human data support the potency of *insulin glulisine* on insulin receptor sites, i.e. its ability to achieve adequate glycemic control, and its sustainability.
4. In terms of efficacy, whether the hypoglycemia precipitated by *insulin glulisine* treatment is proportionate to its glycemic control.
5. How safe and how effective is *insulin glulisine* with sustained administration in humans.

### II. Background

This NDA clinical review pertains to *insulin glulisine*, a recombinant rapid-acting insulin analog, which differs from human insulin by the replacement of asparagine in position B3 by lysine, and lysine at position B29 by glutamic acid. The sponsor suggests that *insulin glulisine* be administered subcutaneously; either 0-15 minutes before or immediately following a meal, in order to provide safe and effective long term glycemic control. The target indication for *insulin glulisine* is the treatment of Type 1, and insulin requiring Type 2, diabetes mellitus in adults.

The sponsor claims that *insulin glulisine*, being a recombinant modification of human insulin, produces identical effects to native insulin in humans but is more rapid and of shorter duration. Therefore, it can be administered in the immediate peri-meal period (instead of 30-45 minutes earlier) for the treatment of diabetes mellitus. With regard to safety and efficacy, it is suggested that *insulin glulisine* is non-inferior to currently marketed insulins in controlling hyperglycemia in patients with diabetes based on the findings of three completed pivotal Phase III clinical trials of 26 weeks duration (with extension of two of them to 52 weeks).

A substantial part of this application supports the dosage and administration claim, namely that *insulin glulisine* can be administered in the immediate peri-meal period instead of 30-45 minutes earlier. To support this claim, *insulin glulisine* was administered 0-15 minutes before meals in the 3 pivotal trials. The 4<sup>th</sup> Phase III clinical trial was a dedicated trial to support the post-meal administration claim.

Two additional aspects of labeling are supported by the clinical trial database:

1. That *insulin glulisine* can be administered via an additional route, namely the CSII pump, based on the 5<sup>th</sup> Phase III clinical trial in this NDA.
2. That *insulin glulisine* can be mixed in the same syringe with NPH, based on a subgroup analysis of one the Phase III trials, Trial 3002 in Type 2 Diabetes.

#### **Other Relevant Information**

The pharmacology review indicated that the binding affinity of *insulin glulisine* to the isolated human insulin receptor was comparable to that of regular human insulin. *Insulin glulisine* had similar activities to those of human insulin on incorporating thymidine into de novo DNA and on the phosphorylation state of the insulin receptor and its substrate. The amino acids substitution in insulin glulisine does not seem to alter its binding to human insulin receptor. The potential mitogenic activity of insulin is related to its interaction of insulin with IGF-1 receptors via a IRS-1 signaling pathway. The metabolic activities of insulin utilize a IRS-2 signaling pathway. *Insulin glulisine* activates IRS-2 more than IRS-1 signaling pathway in several animal and human muscle cells.

Pharmacologic studies in different species showed that insulin glulisine was as effective as insulin lispro and showed a slightly higher total blood glucose-lowering activity than human insulin. Glucodynamic studies of insulin glulisine supported its rapid activity. While the addition of increasing concentrations of — to the insulin glulisine formulation progressively attenuated its rapid time action profile, it is not expected that its brief mixing with human NPH insulin immediately before injection would alter the rapid time action profile of insulin glulisine.

#### **Important Issues with Pharmacologically Related Agents**

Two other short acting human insulin analogs are available in the USA, insulin lispro (Homolog) and Insulin aspart (Novolog). The Agency approved insulin lispro in June 1997 and approved Insulin aspart in June 2000. Both drugs have become popular because of their favorable pharmacokinetics and pharmacodynamic profiles relative to regular human insulin. The weight of evidence and standards of care tend to support the utility of short acting insulin analogs, administered via different subcutaneous delivery systems, in patients with insulin requiring diabetes. This submission of a new short acting insulin analog simulates the prior submissions of other approved ones. The sponsor seeks the Agency's approval of *insulin glulisine* for the same indications and proposes a similar label. Therefore, I shall avoid controversial issues that were once raised about insulin analogs.

### **III. Clinical Pharmacology**

Pharmacokinetic trials have demonstrated that *insulin glulisine* is more rapidly absorbed than regular insulin and therefore has a shorter systemic exposure. The pharmacokinetic findings are corroborated by pharmacodynamic assessments indicating that *insulin glulisine* has a more rapid onset with a shorter duration of action than regular insulin. The pharmacokinetic properties of *insulin glulisine* are consistently displayed across a variety of patient populations in which *insulin glulisine* is intended for clinical use. These populations include adult subjects with Type 1 or Type 2 Diabetes and pediatric (both children and adolescents) subjects with Type 1 Diabetes as well as in otherwise healthy subjects with obesity or impaired renal function. The rapid-acting

properties of *insulin glulisine* were observed when *insulin glulisine* was injected into different anatomical areas generally used for insulin administration (abdomen, thigh and deltoid) and when mixed with NPH in a syringe immediately before injection. Furthermore, the equipotency of *insulin glulisine* to short-acting insulin preparations allows the convenient and safe switching between short-acting insulin preparations and *insulin glulisine* in subjects with diabetes.

#### **Absorption and Bioavailability**

The pharmacokinetic trials in healthy volunteers and in patients with diabetes demonstrated that the absorption of *insulin glulisine* is faster and its peak concentration is higher than regular human insulin. In a trial in patients with Type 1 Diabetes (n=20) after subcutaneous administration of 0.15 IU/kg, the  $T_{max}$  of *insulin glulisine* was 55 minutes and its  $C_{max}$  was 82  $\square$ IU/mL. These compared to a  $T_{max}$  of 82 minutes and a  $C_{max}$  of 46  $\square$ IU/mL for regular human insulin. When *insulin glulisine* was injected subcutaneously into different areas of the body, there was a slightly faster absorption from the abdomen compared to the deltoid or thigh. The absolute bioavailability of *insulin glulisine* after subcutaneous administration is 73% from the abdomen, 71% from the deltoid, and 68% from the thigh.

#### **Distribution and Elimination**

After subcutaneous administration, *insulin glulisine* is eliminated more rapidly than regular human insulin with an apparent half life of 42 minutes for the former and 86 minutes for the latter. After intravenous administration, the volumes of distribution of *insulin glulisine* and regular human insulin are 13 L and 21 L, and their half lives are 13 min and 17 min, respectively.

#### **Pharmacodynamics**

*Insulin glulisine* is clinically equipotent -in terms of glucose lowering activity- to regular human insulin as determined by steady state glucodynamics during the euglycemic clamp in healthy volunteers. Trials in healthy volunteers and in patients with diabetes demonstrated that *insulin glulisine* has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously. In a 6-hour trial in patients with Type 1 Diabetes (n= 20), the glucose-lowering profiles of 0.15 IU/kg doses of *insulin glulisine* and regular human insulin were assessed after various injection times in relation to a standard meal. When *insulin glulisine* was given 2 minutes before the start of a meal and regular human insulin given 30 minutes before the start of the meal, the highest postprandial glucose concentrations were equivalent. However, the lowest glucose concentrations were reached 2 hours earlier after *insulin glulisine* injection. When both *insulin glulisine* and regular human insulin were given 2 minutes before the start of a meal, *insulin glulisine* achieved lower maximal postprandial glucose concentration than regular human insulin. The lowest glucose concentrations after *insulin glulisine* injection were reached 2 hours earlier compared with regular human insulin. When *insulin glulisine* was given 15 minutes after the start of a meal and regular human insulin given 2 minutes before the start of a meal, the highest postprandial glucose concentration and the lowest glucose concentrations after both injections were comparable.

#### IV. Description of Clinical Data

*The information submitted was of good scientific and clinical quality and was adequate to support the sponsor's claims.* Data from Trial 3005 as well as data from two extension trials (3011 and 3012) were not included in the original NDA but were submitted in the 120-day Safety Update. This review integrates the most relevant information from the appended submissions.

The sponsor conducted five controlled Phase III Trials. The trials compared *insulin glulisine* to other widely used short acting insulins, namely insulin lispro (Homolog) in trial 3001, regular human insulin in trials 3002, 3004 and 3005, and insulin aspart (Novolog) in trial 3006. Trials 3001/3011, 3004, and 3006 included patients with Type 1 Diabetes. Trials 3002/3012 and 3005 were conducted in Type 2 Diabetes. Trials 3001, 3002 and 3005 are pivotal to assess the safety and efficacy of *insulin glulisine*. Because a placebo arm is not ethically justifiable, controlled trials include an active comparator insulin of short duration. An overview of the pivotal trials is displayed here.

Pivotal Phase III Clinical Trials

	3001	3002	3005
Population	Type 1 DM adults	Type 2 DM adults	Type 2 DM adults
Region	Europe, South Africa	North America, Australia	Australia, NZ, EU, Isr, S Af
No. treatment arms	2	2	2
Glulisine dosing	s.c. injection 0-15 min before meals	s.c. injection 0-15 min before meals	s.c. injection 0-15 min before, or immediately after, meals
Comparator	Parallel group Active control (lispro)	Parallel group Active control (regular insulin)	Parallel group Active control (regular insulin)
Blinding	No	No	No
Randomization	Central call-in (1:1) Stratified by prestudy use of insulin glargine vs. other basal insulin	Central call-in (1:1) Stratified by prestudy use of OHAs	Central call-in (1:1) Stratified by prestudy use of OHAs
Basal insulin	Insulin glargine once daily	NPH insulin twice daily	NPH insulin twice daily
Duration of treatment	26 weeks	26 weeks	26 weeks
Extension study	3011 (26 weeks)	3012 (26 weeks)	None
No. subjects ITT	672	876	890

#### Subjects Selection

The trials enrolled men and women at least 18 years of age and with screening glycated hemoglobin of  $>6.0\%$  to  $\leq 11.0\%$ . For the purposes of the protocols, Type 1 Diabetes was defined as the onset of diabetes under age 40 and requiring continuous insulin therapy since the time of diagnosis. Type 2 Diabetes was defined as a medical history of diabetes that did not require continuous insulin therapy since the time of diagnosis. Subjects with Type 1 Diabetes were to have received more than 1 year of continuous insulin therapy immediately before trial entry, and subjects with Type 2 Diabetes were required to have received more than 6 months of continuous insulin therapy immediately before trial entry. No insulin-naïve subjects were included in any trial. Within each trial, inclusion and exclusion criteria were as unrestrictive as possible to enable the trial populations to reflect the general population of patients with diabetes. Only those concomitant illnesses or medications that could limit the ability of subjects to safely complete the trial period, confound the evaluation of trial findings, or that conformed to potential

contraindications of insulin therapy, were excluded. Exclusion criteria included active proliferative diabetic retinopathy or other unstable retinopathy, a history of nonhypoglycemia-related seizure disorders, impaired hepatic function (e.g., ALT or AST value greater than  $2 \times$  the upper limit of normal), impaired renal function (e.g., serum creatinine  $>177 \mu\text{mol/L}$ ), previous pancreatectomy, or clinically relevant cardiovascular, hepatic, neurologic, endocrine, active cancer, or other major systemic diseases that may have prevented the subject from completing the trial safely.

### Subjects Exposure

In Type 1 Diabetes, 625 subjects were treated with *insulin glulisine* administered s.c. before meals (Trials 3001/3011 and 3004) and 296 with *insulin glulisine* administered s.c. immediately after a meal (defined as the earlier of the following times: immediately after completing a meal or 20 minutes after starting a meal) (Trial 3004). An additional 29 subjects received *insulin glulisine* by continuous subcutaneous insulin infusion (CSII) (Trial 3006). Therefore, a total of 950 subjects with Type 1 Diabetes received *insulin glulisine* in Trials 3001/3011, 3004, or 3006. In the 3011 extension trial, 302 subjects received *insulin glulisine* and 287 subjects received insulin lispro. In the calculation of overall exposure to trial medication in subjects with Type 1 Diabetes, subjects enrolled in the 3011 extension trial were not counted separately because they were included in the subject count for Trial 3001.

In Type 2 Diabetes, 883 subjects were treated with *insulin glulisine* and 883 received regular insulin (Trials 3002/3012 and 3005). In the 3012 extension trial, 357 subjects received *insulin glulisine* and 352 received regular insulin.

The patients receiving *insulin glulisine* or the active comparator were adequately balanced with respect to their types of insulin regimen and stratified based upon pretrial treatment.

Three pivotal trials (3001, 3002, 3005), including 2438 subjects, lasted for 26 weeks (from randomization). A total of 1298 patients from trials 3001 and 3002 continued to be followed up for a total of 52 weeks to assess the long term safety of *insulin glulisine*. These extension trials are referred to as trials 3011 and 3012, respectively.

### A valid primary efficacy outcome was chosen for the trials

The primary efficacy measure was change from baseline to endpoint in centrally analyzed GHb. The correlation between GHb and HgbA1c measurements is  $>0.97$ . The rationale for using GHb (which measures all glycosylated hemoglobin species) rather than the subspecies HgbA1c as the primary efficacy measure was the lower susceptibility of GHb to degrade over the time required to ship specimens to the single central laboratory from multinational trial sites. GHb results were reported as glycosylated hemoglobin A1c (HbA1c) equivalents and are directly traceable to the Diabetes Control and Complications Trial (DCCT) reference, for which the relationship between mean BG (measured by HbA1c) and the risk for vascular complications has been established.

### Appropriate secondary efficacy variables were assessed

The secondary outcome measures were

1. GHb change
  - a. From BL to wk 12
  - b. From BL to wk 26
2. Self monitored blood glucose (SMBG) profile

3. Symptomatic Hypoglycemia
4. Insulin doses
5. Treatment Satisfaction

Symptomatic hypoglycemia is an objective assessment of hypoglycemia to minimize bias. Symptomatic hypoglycemia was categorized as follows: all symptomatic hypoglycemia, severe symptomatic hypoglycemia, nocturnal symptomatic hypoglycemia, and severe nocturnal symptomatic hypoglycemia. The categorization of symptomatic hypoglycemia was prospectively defined and uniformly applied across all Phase III trials. In the two pivotal efficacy trials, all categories of symptomatic hypoglycemia were evaluated for the following time periods: screening/run-in phase (during which all subjects received the comparator treatment and the trial basal insulin), month 1 of treatment, month 2 to the end of treatment, month 4 to the end of treatment, and the entire treatment phase. Episodes of severe symptomatic hypoglycemia were precisely defined. The definition of severe hypoglycemia was based on features of the definition used in DCCT.

**Primary statistical analysis was based on the ITT population and consistency confirmed in the PP population**

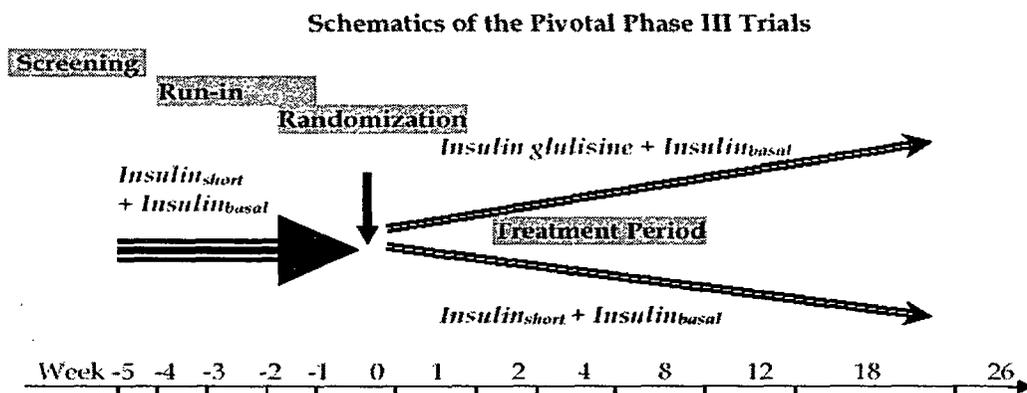
In the efficacy trials involved in this submission, ITT is the primary analysis population. The ITT population was defined as all randomized subjects who received trial treatment. Because the ITT population comprises all randomized and treated subjects, it best reflects the treatment allocation. However, when evaluating noninferiority rather than superiority, the ITT analysis may be biased toward equivalence when noncompliance or poor conduct is involved. The per-protocol (PP) population was a subset of the ITT population and included all randomized and treated subjects with no protocol violations. In evaluating noninferiority, the PP analysis can reveal possible treatment-related differences, even though it can be confounded with postrandomization exclusion bias. With this consideration, to conclude noninferiority, results from both ITT and PP need to be evaluated for consistency.

**To determine noninferiority of  $\Delta \text{GHb}_{\text{insulin glulisine}}$  to  $\Delta \text{GHb}_{\text{comparator}}$  with a margin of 0.4%**

The primary efficacy analysis was to demonstrate the noninferiority of  $\Delta \text{insulin glulisine}$  to  $\Delta \text{comparator}$ , with  $\Delta$  being the change in GHb from baseline to endpoint. The analysis was performed by comparing the upper bound of the 95% confidence interval for the mean difference between *insulin glulisine* and comparators in the change from baseline to endpoint with a predefined noninferiority margin of 0.4% GHb, as agreed upon by the Agency.

The patients maintained a long acting insulin (for basal glycemic control) to which *insulin glulisine* or the active comparator was added. The long acting basal insulin was insulin glargine in Trials 3001 and 3004, and NPH insulin in Trial 3002 and 3005.

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Trial phases were standardized across Phase III efficacy trials and were as follows:

#### Screening/ run-in phase:

Throughout this 4-week phase, all subjects received the same standard regimens of basal and short-acting insulin preparations. The short acting insulin preparation administered throughout the run-in phase was the comparator for each trial (insulin lispro (Homolog) in Trial 3001, and regular insulin in Trials 3002 and 3004). The basal insulin was the same as that to be administered throughout the treatment phase (glargine in Trials 3001 and 3004, and NPH in Trial 3002). The major objectives of the run-in phase were:

- To ensure that all subjects were familiar with the trial procedures, notably with the titration of insulin preparations to meet target BG values
- To acclimatize subjects with any changes in dosing regimens and in the use of a new basal and/or short-acting insulin, where appropriate
- To provide a stable background against which the effects of trial treatment could be evaluated
- To determine the need for continued OHA use while conforming to protocol requirements for the 4-week run-in period, during which subjects received the trial insulin regimen (Trial 3002)
- To confirm subject eligibility for entry into the trial.

Subjects were to be randomized to trial treatment as soon as possible after reaching the end of the 4-week run-in phase, irrespective of whether they had met target BG values.

Following the run-in phase, the duration of randomized treatment in the pivotal efficacy trials was 26 weeks (6 months) and the duration of treatment in Trial 3004 was 12 weeks. These treatment durations, in addition to the preceding 4-week run-in phase, were considered to be sufficient for achieving steady-state conditions, enabling an adequate assessment of time dependent changes in GHb and the concomitant risk of hypoglycemia.

#### Baseline (day 1):

Subjects were randomized to treatment and began their randomized trial treatment regimen. For subjects randomized to *insulin glisine*, the starting dose of *insulin glisine* was to be the same as that of the short-acting insulin preparation at the end of the run-in phase, unless a change in dose was necessitated to meet target BG values while avoiding hypoglycemia, according to the results of the 7-point SMBG profile performed during the week before baseline.

#### Treatment phase:

- Trial 3001 (26 weeks). Visits (including telephone contacts) were scheduled for Weeks 2, 4, 8, 12, 18, 22, and 26
- Trial 3002 (26 weeks). Visits (including telephone contacts) were scheduled for Weeks 1, 2, 3, 4, 6, 8, 12, 18, and 26
- Trial 3004 (12 weeks). Visits (including telephone contacts) were scheduled for Weeks 1, 2, 4, 8, and 12

**Follow-up:**

There was a telephone follow-up for reporting occurrences of symptomatic hypoglycemia and adverse events up to 24 hours after the last injection of trial treatment.

**Open label and potential bias**

Neither the investigators nor the trial subjects were blinded to trial treatments because of: 1) incompatibility between the cartridges and pens for different trial treatments (Trial 3001), 2) major differences in the size and shape of the medication vials and the colors of the gaskets (Trials 3001 and 3002), 3) different premeal injection times for *insulin glulisine* and regular insulin (Trial 3002).

The open-label design of Phase III *insulin glulisine* trials, and the administration of comparator agents in all subjects throughout the run-in phase, is factors intrinsic to the trial design that may have introduced a potential bias in the reporting of certain variables.

**Potential bias against the investigational trial drug:**

There is a potential for over-reporting subjective symptoms (e.g., symptomatic hypoglycemic episodes and injection site reactions) in subjects who receive an unfamiliar investigational agent, such as *insulin glulisine*, relative to the widely utilized short-acting insulin preparations used as comparators in this program. Many subjects may have received the comparator short-acting insulin preparation before trial entry as a part of their usual therapeutic regimen, and all subjects received the comparator throughout the run-in phase before randomization, potentially accentuating the reporting bias against the investigational trial agent because all subjects were familiar with the comparator agent.

The potential bias in favor of the investigational trial drug was minimized by the use of a central computerized telephone randomization system in all trials to avoid potential imbalances in treatment groups due to investigator bias in the assignment of treatments; The primary efficacy measure (change from baseline in total glycosylated hemoglobin [GHb]) in efficacy trials was an objective validated measure of glycemic control. GHb was measured at a central laboratory in all trials and the primary investigators and the trial teams were masked to the results of this centrally measured parameter.

**Insulin administration**

Comparator and basal insulin preparations were dosed according to their respective officially approved documentation. Based on data from Phase I trials, *insulin glulisine* was administered s.c. 0 to 15 minutes before the start of a meal. In one arm of Trial 3004, *insulin glulisine* was also administered immediately postmeal (defined as the earlier of the following times: immediately after completing a meal or 20 minutes after starting a meal). For short-acting trial treatments, the recommended anatomical area for s.c. injection was the abdomen.

In Trial 3002, mixing of *insulin glulisine* or regular insulin with NPH was permitted, based on the preference of the individual investigator and subject. The results of a clinical pharmacology trial demonstrated that *insulin glulisine* mixed with NPH immediately before injection produced some attenuation in the peak concentration of *insulin glulisine*, but the time to peak and the total bioavailability of *insulin glulisine* were not affected (Trial 1012). When *insulin glulisine* was mixed with NPH in Trial 3002, *insulin glulisine* was to be drawn into the syringe first (as recommended in the officially approved

documentation for regular insulin and insulin lispro), and the solution was to be injected immediately after mixing.

The short-acting insulin dosage was adjusted in an individualized manner to reach target 2-hour postprandial glucose values, which were uniformly applied across trials and based on generally accepted clinical practice guidelines. In all countries outside North America, self-monitored BG (SMBG) measurements were performed using a whole blood-referenced meter, and the target values were 6.7 to 8.9 mmol/L (120 to 160 mg/dL). In Canada and the USA, SMBG monitoring was performed using a plasma-referenced meter and the target BG values were 7.1 to 9.6 mmol/L (128 to 172 mg/dL). After accounting for the different glucose values obtained using whole blood and plasma determinations, these BG targets were identical. All values were converted to whole-blood parameters for data presentation. Titration of basal insulin was carried out as needed to meet prespecified targets and to enable the effect of each short-acting insulin treatment to be more readily detected.

#### **Demographic and disease characteristics**

In general, treatment groups were well balanced in the pooled analyses. However, *insulin glulisine* subjects had a longer duration of diabetes and duration of previous insulin therapy compared with comparator subjects. There were slightly more men than women, and the majority (>90%) of subjects were white. For subjects with Type 1 Diabetes, the mean age was 40.0 years for *insulin glulisine* and 39.3 years for pooled comparator subjects (overall range 18 to 74 years), and for subjects with Type 2 Diabetes, the mean age was 59.4 years for *insulin glulisine* and 58.8 years for regular insulin subjects (overall range 26 to 87 years). A total of 274 subjects (14.9%) who received *insulin glulisine* and 285 (18.7%) who received comparators in Phase III trials were aged  $\geq 65$  years, and 49 (2.7%) *insulin glulisine* and 30 (2.0%) comparator subjects were aged  $\geq 75$  years. Most subjects  $\geq 65$  years of age and all subjects  $\geq 75$  years of age were in trials of Type 2 Diabetes.

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**Table 7 – Demographics and other background characteristics  
(Studies 3001/3011, 3002/3012, 3004, 3005, and 3006) (ITT population)**

	Type 1 diabetes		Type 2 diabetes		All studies		
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators	
No. ITT subjects	950	641	883	883	1833	1524	
<b>Geographical region</b>							
North America	n (%)	492 (51.8)	235 (36.7)	377 (42.7)	374 (42.4)	869 (47.4)	609 (40.0)
Europe	n (%)	327 (34.4)	325 (50.7)	184 (20.8)	175 (19.8)	511 (27.9)	500 (32.8)
Australia	n (%)	90 (9.5)	43 (6.7)	84 (9.5)	91 (10.3)	174 (9.5)	134 (8.8)
South Africa	n (%)	41 (4.3)	38 (5.9)	53 (6.0)	56 (6.3)	94 (5.1)	94 (6.2)
<b>Sex</b>							
Male	n (%)	525 (55.3)	342 (53.4)	460 (52.1)	445 (50.4)	985 (53.7)	787 (51.6)
Female	n (%)	425 (44.7)	299 (46.6)	423 (47.9)	438 (49.6)	848 (46.3)	737 (48.4)
<b>Age (years)</b>							
Mean (SD)		40.0 (11.91)	39.3 (12.09)	59.4 (9.65)	58.8 (9.81)	49.3 (14.54)	50.6 (14.49)
≥65	n (%)	20 (2.1)	14 (2.2)	254 (28.8)	271 (30.7)	274 (14.9)	285 (18.7)
≥75	n (%)	-	-	49 (5.5)	30 (3.4)	49 (2.7)	30 (2.0)
<b>BMI (kg/m<sup>2</sup>)</b>							
Mean (SD)		25.33 (4.285)	25.91 (4.344)	33.01 (6.261)	32.73 (6.288)	29.55 (6.290)	29.86 (6.492)
BMI >28	n (%)	281 (29.6)	176 (27.5)	689 (78.0)	681 (77.1)	970 (52.9)	857 (56.2)
<b>Race</b>							
White	n (%)	910 (95.8)	609 (95.0)	777 (88.0)	786 (89.0)	1687 (92.0)	1395 (91.5)
Black	n (%)	12 (1.3)	12 (1.9)	66 (7.5)	62 (7.0)	78 (4.3)	74 (4.9)
Asian/Oriental	n (%)	10 (1.1)	8 (1.2)	21 (2.4)	20 (2.3)	31 (1.7)	28 (1.8)
Multiracial	n (%)	18 (1.9)	12 (1.9)	19 (2.2)	15 (1.7)	37 (2.0)	27 (1.8)
<b>Hispanic ethnicity<sup>a</sup></b>							
	n (%)	21 (2.2)	11 (1.7)	68 (7.7)	70 (7.9)	89 (4.9)	81 (5.3)

<sup>a</sup> Data collected in Studies 3002/3012, 3004, and 3005 only, independent of race (a subject with Hispanic ethnicity was also assigned to any one category of race).

Data presented for Studies 3001/3011 and 3002/3012 are for the baseline visit of Study 3001 and 3002, respectively.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3005 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

p3dm0011

For most demographic variables, there were no noteworthy differences between treatments in the pooled data presentations. However, there was a statistically significant difference between treatments in mean age in Trial 3002/3012: subjects in the *insulin glulisine* group were older than those in the regular insulin group (mean age 58.9 versus 57.7 years). Accordingly, more *insulin glulisine* than comparator subjects in this trial were ≥65 years of age: 29.2% *insulin glulisine* versus 25.6% regular insulin. Additionally, 6.2% *insulin glulisine* versus 3.4% regular insulin subjects were ≥75 years of age.

#### Diabetic history

For subjects with Type 1 Diabetes, the mean age at diagnosis of diabetes was 21.2 years for *insulin glulisine* and 21.9 years for the comparator group (range 0 to 65 years), and for subjects with Type 2 Diabetes, the mean age at diagnosis was 45.8 years for *insulin glulisine* and 45.9 years for the comparator group (range 15 to 79 years). Subjects with Type 1 Diabetes had received previous insulin treatment for a mean of 19.1 years in the *insulin glulisine* group and 17.6 years in the pooled comparator group (range 0 to 64 years), and subjects with Type 2 Diabetes had received previous insulin treatment for a mean of 6.4 years in the *insulin glulisine* group and 5.8 years in the comparator group (range 0 to 38 years). Fewer than 5% of subjects in

any pooled treatment group had autonomic neuropathy at baseline.

**Table 8 – Diabetic history at baseline (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006) (ITT population)**

Characteristic	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
No. ITT subjects	950	641	883	883	1833	1524
<b>Time since diagnosis of diabetes (y)</b>						
Mean (SD)	19.3 (11.39)	17.8 (11.07)	14.1 (7.87)	13.4 (7.42)	16.8 (10.18)	15.2 (9.38)
<b>Age at diagnosis of diabetes (y)</b>						
Mean (SD)	21.2 (11.51)	21.9 (11.34)	45.8 (10.05)	45.9 (9.91)	33.1 (16.36)	35.9 (15.85)
<b>Duration of previous insulin treatment (y)</b>						
Mean (SD)	19.1 (11.40)	17.8 (11.12)	6.4 (6.05)	5.8 (5.50)	13.0 (11.18)	10.7 (10.17)
<b>Previous glargine use</b>						
n (%)	210 (22.1)	139 (21.7)	18 (2.0)	26 (2.9)	228 (12.4)	165 (10.8)
<b>Autonomic neuropathy at baseline</b>						
n (%)	46 (4.8)	21 (3.3)	39 (4.4)	39 (4.4)	85 (4.6)	60 (3.9)
<b>OHA use<sup>a</sup></b>						
n (%)	NA	NA	396 (44.8)	411 (46.5)	NA	NA

<sup>a</sup> OHA use data were collected at randomization in Studies 3002/3012 and 3005 only. In those studies, subjects were stratified by use of OHAs at the time of randomization.

NA, not applicable.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart), Type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

p3dm0021

The time since diagnosis of diabetes and the mean duration of previous insulin treatment was greater in *insulin glulisine* than comparator subjects in the pooled analyses of trials in Type 1 or Type 2 Diabetes. In some individual trials, there were statistically significant differences between treatments for diabetic history. In trial 3001/3011, subjects randomized to *insulin glulisine* had a statistically significantly longer time since diagnosis of diabetes (mean time of 17.4 versus 15.6 years) and a longer duration of previous insulin therapy (duration of 17.1 versus 15.3 years). These differences were also present in the subset of subjects who continued into the 3011 extension trial. In trial 3002/3012, subjects randomized to *insulin glulisine* had a statistically significantly longer time since diagnosis (mean time of 14.7 versus 13.4 years), and a significantly longer duration of previous insulin therapy (duration of 7.1 versus 6.4 years) or previous OHA treatment (duration of 13.1 versus 11.8 years).

#### Glycemic control at baseline

Baseline glycemic control was defined by GHb at the time of randomization. Overall, mean baseline GHb was comparable between treatments.

**Table 9 – Glycemic control at baseline: GHb (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006) (ITT population)**

Parameter	Baseline GHb (%)					
	Type 1 diabetes		Type 2 diabetes		All studies	
	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
No. ITT subjects	917	621	859	859	1776	1480
<b>GHb at baseline (%)</b>						
Mean (SD)	7.64 (0.936)	7.58 (0.901)	7.57 (0.920)	7.51 (0.921)	7.61 (0.929)	7.54 (0.913)

Data presented for Studies 3001/3011 and 3002/3012 are for the baseline visit of Study 3001 and 3002, respectively.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin),

Study 3006 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

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## Overview of Individual Phase III Trials

### Study number 3001

Trial 3001 was conducted to support the claim that *insulin glulisine* is a safe and efficacious insulin analog for the control of hyperglycemia in patients with diabetes. This was a pivotal efficacy trial in subjects with Type 1 Diabetes, and was an open, multicenter, centrally randomized, and controlled 2-armed trial of 26 weeks' duration. *Insulin glulisine* and insulin lispro (Homolog) were administered 0 to 15 minutes before meals. Subjects received glargine as the basal insulin. All subjects participated in a 4-week run-in phase during which they received glargine and insulin lispro (Homolog) to familiarize themselves with the dosing regimen and to begin titrating their insulin doses to the target BG levels specified in the protocol. For subjects randomized to *insulin glulisine*, the starting dosage was to be the same as that of insulin lispro (Homolog) at the end of the run-in phase, unless a change was necessitated to meet the target

BG values while avoiding hypoglycemia, according to the results of the 7-point glucose profile performed during the week before baseline. Subjects who completed the 26 weeks of treatment were intended to enroll in the extension Trial 3011.

### Extension Study 3011

This was a 26-week, multinational, multicenter, open, clinical extension trial to assess one year safety of *insulin glulisine* compared with insulin lispro (Homolog) injected subcutaneously in subjects with Type 1 Diabetes also using insulin glargine, and previously participating in trial 3001. It was conducted between Feb 2002 and Feb 2003 in Europe and South Africa. The primary objective of the trial was to evaluate long-term (1 year) safety data in subjects with Type 1 Diabetes exposed to *insulin glulisine*. The secondary objectives were to compare *insulin glulisine* with insulin lispro (Homolog) in terms of the change in glycohemoglobin (GHb), blood glucose (BG) parameters, hypoglycemia and insulin doses in subjects with Type 1 Diabetes. There were to be a total of 3 clinic visits in the 26 weeks of this trial, and a telephone follow-up visit 24 hours after the last (third) clinic visit. Both *insulin glulisine* and insulin lispro (Homolog) were individually dosed as appropriate by subcutaneous (s.c.) injection 0 to 15 minutes before meals. Either *insulin glulisine* or insulin lispro (Homolog) were to be taken in combination with insulin glargine (by s.c. injection once daily, individually titrated) as part of an intensified insulin regimen.

### Study 3002

Trial 3002 was a pivotal efficacy trial in subjects with Type 2 Diabetes, and was an open, multicenter, centrally randomized, and controlled 2-armed trial of 26 weeks' duration. *Insulin glulisine* was administered 0 to 15 minutes before meals, and regular insulin was administered 30 to 45 minutes before meals. Subjects received NPH as the basal insulin. *In this study, insulin glulisine or regular insulin could*

be mixed with NPH within 2 minutes before injection. All subjects participated in a 4-week run-in phase during which they received NPH and regular insulin to familiarize themselves with the dosing regimen and to begin titrating their insulin doses to the target BG levels specified in the protocol. For subjects randomized to *insulin glulisine*, the starting dosage was to be the same as that of regular insulin at the end of the run-in phase, unless a change was necessitated to meet the target BG values while avoiding hypoglycemia, according to the results of the 7-point glucose profile performed during the week before baseline. Subjects who completed the 26 weeks of treatment were intended to enroll in the extension Trial 3012.

#### **Extension Study 3012**

This was a 26-week, multinational, multicenter, open, clinical extension trial to assess the one year safety of *Insulin glulisine* compared with regular human insulin injected subcutaneously in subjects with Type 2 Diabetes mellitus also using NPH insulin, and previously participating in trial 3002. It was conducted between Feb 2002 and April 2003 in North America and Australia. There were to be a total of 3 clinic visits in the 26 weeks of this trial, and a telephone follow-up visit 24 hours after the last (third) clinic visit. The trial enrolled all subjects who successfully completed 26 weeks of trial 3002 and who agreed to continue in the extension trial. *Insulin glulisine* or regular human insulin individually dosed as appropriate by subcutaneous (s.c.) injection. *Insulin glulisine* was to be taken 0 to 15 minutes prior to the meal and regular human insulin was to be injected 30 to 45 minutes prior to the meal. Either *insulin glulisine* or regular human insulin was to be taken in combination with NPH insulin (by s.c. injection, individually titrated) as part of an intensified insulin regimen.

#### **Study 3005**

26-week, multinational, multicenter, controlled, open, 1:1 randomized, parallel clinical trial to assess noninferiority between HMR1964 and regular human insulin injected subcutaneously in subjects with Type 2 Diabetes mellitus also using NPH insulin.

It was performed between Dec 2001 and Jul 2003 in Australia/New Zealand, Europe, Israel, South Africa, and Argentina.

*Insulin glulisine* or regular insulin at least twice daily individually dosed as appropriate by subcutaneous (s.c.) injection. *Insulin glulisine* was administered s.c. 0-15 minutes before meals 2-3 times/day. Human regular insulin was administered in the same way but earlier (30-45 minutes before meals). The doses were individualized to each patient based on 2-hour postprandial WB glucose levels (target 120-160 mg/dl, avoiding hypoglycemia). Either *insulin glulisine* or regular insulin were to be taken in combination with NPH insulin twice daily (individually titrated by s.c. injection) as part of a basal/bolus insulin regimen.

#### **Postmeal administration of *insulin glulisine*: Study 3004**

The main objective of Trial 3004 was to evaluate the safety and efficacy of *insulin glulisine* administered immediately after meals in comparison with the standard premeal timing of administration of both *insulin glulisine* and human regular insulin. It was an open, multicenter, centrally randomized, controlled three-armed trial of 12 weeks' duration in subjects with Type 1 Diabetes. *Insulin glulisine* was administered 0 to 15 minutes before meals or immediately after meals, and regular insulin was administered 30 to 45 minutes before meals. Subjects received glargine as the basal insulin. All subjects participated in a 4-week run-in phase during which they received glargine and regular insulin to familiarize themselves with the dosing regimen and to begin titrating their insulin doses to the target BG levels specified in the protocol. For subjects randomized to *insulin glulisine*, the starting dosage was to be the same as that of regular insulin at the end of the run-in phase, unless a change was necessitated to meet the target BG values

while avoiding hypoglycemia, according to the results of the 7-point glucose profile performed during the week before baseline.

**Continuous Subcutaneous Insulin Infusion: Study 3006**

This was a 12-week, multinational, multicenter, controlled, open, 1:1 randomized, parallel clinical trial comparing the safety of *insulin glulisine* and Insulin aspart (Novolog) used in continuous subcutaneous insulin infusion (CSII) in subjects with Type 1 Diabetes. It was conducted between May 2002 and December 2002 in multiple European countries. It included a screening 4-week run-in phase, and a treatment period of 12 weeks. The Trial compared the safety and compatibility of *insulin glulisine* and Insulin aspart (Novolog) when used in external pumps in terms of catheter occlusions, GHb assessment, insulin doses, blood glucose (BG) parameters, hypoglycemic episodes, unexplained hyperglycemia, adverse events, laboratory data, and vital signs. Both *insulin glulisine* and Insulin aspart (Novolog) were individually titrated and administered in a basal and bolus fashion by an external insulin pump.

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## VI. Integrated Review of Efficacy

### Main results of the pivotal trials

- *Insulin glulisine* is noninferior to human regular insulin or to insulin lispro (Homolog) in subjects with Type 1 or Type 2 Diabetes, based on changes from baseline to endpoint in GHb.
- The overall risk of all categories of symptomatic hypoglycemia does not differ between *insulin glulisine* and short-acting insulin comparators in subjects with Type 1 or Type 2 Diabetes.
- *Insulin glulisine* produced equivalent glycemic control to the active comparator with continued administration for up to one year.
- The efficacy of *insulin glulisine* appears to be maintained irrespective of BMI, age, sex, race, Hispanic ethnicity, baseline degree of glycemic control, or in the absence or presence of concomitant OHAs. However, the small numbers of subjects in any category of race other than white, and the few subjects of Hispanic ethnicity, limits the interpretation of results within these particular subgroups.

### Study 3001

A total of 672 (339 *insulin glulisine*, 333 insulin lispro) subjects were randomized and treated at 67 centers in Europe and South Africa between July 5, 2001 and August 5, 2002. The mean age was 38.5 years, and 96.6% of subjects were white. While the population as a whole was generally balanced between treatments, there was a baseline discrepancy for diabetic history: *insulin glulisine* subjects had a mean duration of diabetes and previous insulin treatment about 2 years longer than insulin lispro (Homolog) subjects. The mean duration of randomized trial treatment was 181.6 days in the *insulin glulisine* group and 179.2 days in the insulin lispro (Homolog) group. The primary efficacy measure in this trial was the analysis of change from baseline to endpoint in GHb using the ITT population. To assess noninferiority, the upper bound of the confidence interval (CI) was compared with the predefined noninferiority margin of 0.4% GHb. Based on the predefined noninferiority margin of 0.4%, the noninferiority of *insulin glulisine* compared with insulin lispro (Homolog) was shown by the fact that the upper bound of the 95% CI was below 0.4%. Efficacy findings are summarized in the following table.

Treatment (ITT evaluable subjects)	GHb (%)		Symptomatic hypoglycemia Mean rate/month <sup>b</sup>		Adjusted mean daily insulin dose (IU) Change from baseline at endpoint <sup>c</sup>		
	Baseline	Change at endpoint	All	Severe	Rapid -acting	Basal	Total
	Mean	Adjusted mean <sup>a</sup>					
<b>ITT population</b>							
Glulisine (N=339)	7.60	-0.14	3.64	0.03	-1.07	0.12	-0.86
Lispro (N=333)	7.58	-0.14	3.48	0.02	-0.81	1.82	1.01
Difference glulisine- lispro	Change at endpoint Difference: 0.00 95% CI (-0.09, 0.10) p=0.9329 <sup>d</sup>		p=0.7435	p=0.2438	p=0.5632	p=0.0001	p=0.0123

The results of Trial 3001 show that *insulin glulisine* was noninferior to insulin lispro (Homolog) for glycemic control, as assessed by changes in GHb. There was no relevant difference between

treatments in the reporting of all types of symptomatic hypoglycemia. Results from quality of life questionnaires corroborated the finding of a similar perception of hypoglycemia in *insulin glulisine* and insulin lispro (Homolog) treated subjects. No noteworthy differences in treatment-emergent adverse events possibly related to the trial drug were detected between treatments. While more *Insulin glulisine* than insulin lispro (Homolog) subjects reported musculoskeletal/connective tissue disorders and cardiac events, there was no evidence suggesting that these TEAEs were related to *insulin glulisine* or *insulin glulisine*-induced hypoglycemia.

### Study 3011

A total of 589 (87.6%) subjects continued treatment in the 26-week extension trial 3011 (302 on *insulin glulisine* and 287 on insulin lispro). 10 (1.7%) subjects withdrew during the 26-week extension trial (5, 1.7% in each treatment group) and 33 (4.9%) withdrew during the entire 52-week treatment phase (15, 4.4% *insulin glulisine*; 18, 5.4% insulin lispro). The median duration of treatment was 365 days in the 52-week treatment phase and 182 days in the 26-week extension trial and was similar in the two treatment groups. The mean age of the population was 38.5 years at the 52-week baseline. 97% of subjects were white. Except for the discrepancy noted at baseline for Trial 3001, the population as a whole was generally balanced between the two treatment groups in terms of demographic and diabetes disease characteristics.

All results were analyzed using two time periods, the 26-week extension trial (extension trial 3011) and the 52-week treatment phase (trials 3001 and 3011 combined). The reduction of GHb levels decreased in the first 26 weeks of the trial period (*insulin glulisine*: -0.15%; insulin lispro: -0.13%) was followed by an increase in GHb in both treatment groups in the 26-week extension trial (*insulin glulisine*: 0.14%; insulin lispro: 0.15%) such that endpoint GHb values were similar to those at the 52-week baseline in both treatment groups (change from 52-week baseline to endpoint: *insulin glulisine*: -0.02%; insulin lispro: -0.00%). The mean daily total insulin dose increased from the 52-week baseline to the endpoint of the 52-week period by 1.71 IU in the insulin lispro (Homolog) group compared to a decrease of 0.30 IU in the *Insulin glulisine* group. This difference was mostly influenced by the larger increase in the basal insulin dose in the insulin lispro (Homolog) group (+2.01 IU compared to +0.21 IU in the *insulin glulisine* group). Self-monitored 8-point BG profiles were generally similar without clinically relevant differences in the two treatment groups at the 52-week baseline and throughout the 52-week treatment period. During the 52-week treatment period, both the frequency and the monthly rate were similar between the two treatment groups for all types of symptomatic hypoglycemia. The frequency of all types of hypoglycemia decreased in the 26-week extension trial in both treatment groups.

Both *insulin glulisine* and insulin lispro (Homolog) were well tolerated. Safety findings in the 26-week extension trial generally reflected those observed during the entire 52-week treatment period. The type and frequency of treatment emergent adverse events (TEAEs) were generally similar for the two treatment groups, however, reporting of cardiac TEAEs was much lower in *insulin glulisine* subjects during the 26-week extension trial (1 subject, 0.3%) than in the initial 26-week period of the 52-week treatment period (9 subjects, 2.7%). During the 52-week treatment phase, a total of 474 (70.5%) subjects had at least one reported TEAE: 245 (72.3%) *insulin glulisine* subjects and 229 (68.8%) insulin lispro (Homolog) subjects. As stipulated by the protocol all severe hypoglycemic events were automatically classified as a serious TEAE and were reported in 48 (14.2%) *insulin glulisine* subjects and 38 (11.4%) insulin lispro (Homolog) subjects. Nonhypoglycemia related TEAEs were reported in 33 (9.7%) *insulin glulisine* subjects and 21 (6.3%) insulin lispro (Homolog) subjects. One death occurred in a *insulin glulisine* subject that was not considered to be due to trial medication. No noteworthy differences were

noted during the 52-week treatment period between treatment groups in the reporting of diabetic ketoacidosis -ketosis, injection site TEAEs or potential systemic hypersensitivity reactions. Either minimal or no increases were seen in all categories of anti-insulin antibodies in *insulin glulisine* treated subjects.

### Study 3002 Results

A total of 876 (435 *insulin glulisine*, 441 regular insulin) subjects were randomized and treated at 89 centers in Australia, Canada, and the USA between 2 July, 2001 and 18 October, 2002. The mean age was 58.3 years, and 85.4% of subjects were white. The population as a whole was generally balanced between treatments except that 1) the mean age of subjects in the *insulin glulisine* group was approximately 1 year older than those in the regular insulin group; 2) *insulin glulisine* subjects had a mean duration of diabetes 1.3 years longer, and a previous insulin treatment 0.7 years longer, than regular insulin subjects; 3) the mean duration of previous OHA use was significantly longer in the *insulin glulisine* group. The mean duration of randomized trial treatment was 177.6 days in the *insulin glulisine* group and 175.5 days in the regular insulin group. *Approximately 78% of subjects mixed their short acting insulin preparation with NPH at some time during the study.*

Treatment (ITT evaluable subjects)	GHb (%)		Symptomatic hypoglycemia Mean rate/month <sup>b</sup>		Adjusted mean daily insulin dose (IU) Change from baseline at endpoint <sup>c</sup>		
	Baseline	Change at endpoint	All	Severe	Short- acting	Basal	Total
	Mean	Adjusted mean <sup>a</sup>					
ITT population							
Glulisine (N=435)	7.57	-0.46	1.23	0.01	3.69	5.73	9.33
Regular insulin (N=441)	7.50	-0.30	1.34	0.02	5.00	6.63	11.10
Difference glulisine- regular insulin	Change at endpoint Difference: -0.16 95% CI (-0.26, -0.05) p=0.0029 <sup>d</sup>		p=0.6949	p=0.2547	p=0.1756	p=0.7741	p=0.2427

The trial established the noninferiority of *insulin glulisine* compared with regular insulin by the fact that the upper bound of the 95% CI was below 0.4%. In fact, the upper limit of the 95% CI was below zero, suggesting statistical superiority in the ITT population. There were no differences between the treatment arms in the change from baseline in insulin dose nor in the rates of symptomatic hypoglycemia for both *insulin glulisine* and regular insulin. There were no specific safety concerns in this trial. *The efficacy of insulin glulisine was observed when used in combination with OHAs. In addition, the efficacy of insulin glulisine was observed when immediately premixed with NPH in a syringe before injection.* Thus, this trial demonstrates that *insulin glulisine* is well tolerated and effective compared with regular human insulin in subjects with Type 2 Diabetes.

### Study 3012 Results

A total of 709 (80.9%) subjects continued treatment in the 26-week extension trial 3012 (357 on *insulin glulisine* and 352 on regular insulin). 42 (5.9%) subjects withdrew during the 26-week extension phase (28, 7.8% *insulin glulisine*, 14, 4.0% regular insulin) and 106 (12.1%) withdrew during the entire 52-week treatment phase (56, 12.9% *insulin glulisine*; 50, 11.3% regular insulin). The median duration of treatment was 364 days in the 52-week treatment phase and 182 days in the 26-week extension phase and was similar in the two treatment groups. The mean age of the population was 58.3 years at the 52-week baseline. 85% of subjects were white. Except as noted at baseline in Trial 3002, the population was generally balanced between the two treatment groups in terms of demographic and diabetes disease characteristics.

All results were analyzed using two time periods, the 52-week treatment phase (trials 3002 and 3012 combined) and the 26-week extension treatment phase (extension trial 3012). The reduction in GHb levels in the initial 26 weeks of the 52-week treatment phase (*insulin glulisine*: -0.44%; regular insulin: -0.29%) was followed by an increase in GHb in both treatment groups in the 26-week extension phase (+0.26% *insulin glulisine*, +0.19% regular insulin). At endpoint, the GHb values were lower than at the 52-week baseline, with the greater reduction seen in *insulin glulisine* subjects (*insulin glulisine*: -0.23%; regular insulin: -0.13%). At endpoint of the 52-week treatment phase, the mean daily basal, short-acting and total insulin dose increased in both treatments with larger increases seen in the regular insulin group. Basal daily insulin dose increased in both treatments by 6.11 IU in *insulin glulisine* subjects and 9.07 IU in regular insulin subjects. Short-acting daily dose increased in both treatment groups (4.68 IU *insulin glulisine*, 5.65 IU regular insulin). The total daily insulin dose increased in both the *insulin glulisine* group (10.79 IU) and the regular insulin group (14.83 IU). Self-monitored 7-point BG profiles were similar in the two treatment groups at the 52-week baseline. Values from the BG profiles were lower at all time points in *insulin glulisine* treated subjects throughout the 52-week treatment period. With regards to all symptomatic hypoglycemia, a similar incidence (77.2% *insulin glulisine*, 76.6% regular) and mean monthly rate (*insulin glulisine*: 0.98, regular: 1.11) of was seen in both treatments. A similar incidence of nocturnal symptomatic hypoglycemia was seen between treatments. The incidence of severe and severe nocturnal hypoglycemia was low in both groups. While more *insulin glulisine* subjects experienced severe symptomatic hypoglycemic episodes as compared to regular insulin subjects, the rate of severe hypoglycemia was lower in *insulin glulisine* subjects relative to regular insulin subjects. The incidence and rate of severe nocturnal hypoglycemia was similar between treatments.

Both *insulin glulisine* and regular insulin were well tolerated. Five subjects died during the 52-week treatment phase: 2 in the *Insulin glulisine* group (1 subject with hemorrhagic shock associated with myocardial infarction and 1 subject due to subdural hematoma associated with cerebral herniation and respiratory arrest) and 3 in the regular insulin group (2 subjects due to cardiac arrest and 1 due to pulmonary embolism). In addition, 1 regular insulin subject died 20 days after the end of trial treatment (non TEAE). None of the deaths were deemed to be related to trial medication or hypoglycemia. Safety findings in the 26-week extension trial generally reflected those observed during the entire 52-week treatment period. No noteworthy differences were noted during the 52-week treatment period between treatment groups in the reporting of diabetic ketoacidosis, injection site TEAEs or potential systemic hypersensitivity reactions. Either minimal or no increases were seen in all categories of anti-insulin antibodies in *insulin glulisine* treated subjects.

### Study 3005 Results

1088 subjects entered the screening phase, of which 892 were randomized and 890 received trial medication: 448 *insulin glulisine* subjects and 442 regular insulin subjects were randomized and treated. Of the 890 subjects treated, 42 subjects (28 *insulin glulisine*, 14 regular insulin) were withdrawn after the start of treatment. The ITT population was defined as all subjects randomized and treated, and consisted of 890 subjects. The PP population was defined as all ITT subjects excluding subjects with a major protocol violation, and consisted of 795 subjects. The mean age of the population was 59.9 years and 91.6% were white. The population as a whole was generally balanced between the two treatment groups in terms of demographic and diabetes disease characteristics at trial entry.

The primary objective of the trial, to demonstrate noninferiority of *insulin glulisine* compared to regular insulin in the change in GHb from baseline to endpoint, was demonstrated by the fact that the upper bound of the 95% confidence interval (CI) was below 0.4% (95% CI: -0.07, 0.13). No noteworthy differences were noted between the treatment groups in the frequencies and monthly rates of all symptomatic hypoglycemia. At endpoint, both treatment groups had increased their insulin doses. BG values from the self monitored 7-point profiles were similar at all 7 time points in both treatment groups, except for the 2-hour post-breakfast values, for which the BG values were significantly lower in the *insulin glulisine* group ( $p=0.0001$ ). The use of OHAs at randomization was a stratification variable and 33.6% of subjects were receiving OHAs at randomization. No differences were detected between treatments in the change in GHb from baseline or in the incidence of any type of symptomatic hypoglycemia between the treatment groups for those subjects receiving OHAs at randomization and those not receiving OHAs. Both *insulin glulisine* and regular insulin were well tolerated. The type and frequency of treatment emergent adverse events (TEAEs) were generally similar for the two treatment groups. A total of 520 (58.4%) subjects had at least one reported TEAE: 260 (58.0%) *insulin glulisine* subjects and 260 (58.8%) regular insulin subjects. Serious TEAEs were reported in 95 (10.7%) subjects: 43 (9.6%) *insulin glulisine* subjects and 52 (11.8%) regular insulin subjects. No noteworthy differences were noted between treatment groups in the reporting of serious hypoglycemic events, cardiac disorders, eye disorders, diabetic ketoacidosis, injection site reactions and potential systemic hypersensitivity reactions. Three deaths occurred in the trial (2 in the *insulin glulisine* group: 1 due to a hemorrhagic intracerebral/intraventricular accident and 1 due to bleeding of esophageal varices; and 1 in a subject receiving regular insulin due to aspiration). None of the deaths were deemed to be possibly related to trial medication nor were they associated with a severe hypoglycemic event. No clinically noteworthy between treatment differences were noted in clinical laboratory values or vital signs. During the treatment phase, the *insulin glulisine* group reported a somewhat greater improvement in their Treatment Satisfaction scores than in the regular insulin group, and similar improvements in perceived frequencies of hyper- and hypoglycemia.

### Study 3004 Results

A total of 860 (286 premeal *insulin glulisine*, 296 postmeal *insulin glulisine*, and 278 regular insulin) subjects were randomized and treated at 93 centers in Australia, Canada, and the USA between 25 September, 2001 and 6 September, 2002. The mean age was 40.3 years, and 94.3% of subjects were white. The population was well balanced between treatments in terms of demographic and diabetes disease characteristics. The mean duration of randomized trial treatment was 83.4 days in the premeal *insulin glulisine* group, 82.9 days in the postmeal *insulin glulisine* group, and 80.3 days in the regular insulin group. The primary efficacy measure in this trial was the analysis of change from baseline to endpoint in GHb. The main findings are tabulated as follows:

Treatment (ITT evaluable subjects)	GHb (%)		Symptomatic hypoglycemia Mean rate/month <sup>b</sup>		Adjusted mean daily insulin dose (IU) Change from baseline at endpoint <sup>c</sup>		
	Baseline	Change at endpoint	All	Severe	Short- acting	Basal	Total
	Mean	Adjusted mean <sup>a</sup>					
<b>ITT population</b>							
Glulisine premeal (N=286)	7.73	-0.26	3.46	0.05	-0.88	0.99	0.04
Glulisine postmeal (N=296)	7.70	-0.11	3.71	0.05	-0.47	0.24	-0.22
Regular insulin (N=276)	7.64	-0.13	3.49	0.13	1.75	0.65	2.35
Change at endpoint:							
Postmeal glulisine-regular:	Difference: 0.02 98.33% CI (-0.11; 0.16) p= 0.6698 <sup>d</sup>		p=0.7462	p=0.2566	p=0.0012	p=0.3630	p=0.0014
Premeal glulisine-regular:	Difference: -0.13 98.33% CI (-0.26; 0.01) p= 0.0234 <sup>d</sup>		p=0.8079	p=0.2093	p=0.0001	p=0.4420	p=0.0042
Postmeal glulisine- premeal glulisine	Difference: 0.15 98.33% CI (0.02; 0.29) p= 0.0062 <sup>d</sup>		p=0.5662	p=0.9014	p=0.5451	p=0.0896	p=0.7414

The primary objectives of the trial were achieved: the noninferiority of postmeal *insulin glulisine* to regular insulin and to premeal *insulin glulisine* in the change from baseline to endpoint in GHb was demonstrated. Additionally, the noninferiority of premeal *insulin glulisine* to regular insulin was demonstrated. Based on the predefined noninferiority margin of 0.4%, the noninferiority of postmeal *insulin glulisine* to premeal *insulin glulisine* and to regular insulin, and the noninferiority of premeal *insulin glulisine* to regular insulin, was shown by the 98.33% CI values. Statistically significant reductions from baseline in GHb were observed in all three treatment groups. Postmeal *Insulin glulisine* was well tolerated. There were no noteworthy differences in the reporting of safety parameters between postmeal *insulin glulisine* and the premeal *insulin glulisine* or regular insulin groups, or in a pooled analyses of *insulin glulisine* subjects compared with regular insulin subjects.

### Study 3006 Results

A total of 72 subjects entered the screening phase, of which 59 were randomized all of whom received trial medication. There were 29 *insulin glulisine* subjects and 30 Insulin aspart (Novolog) subjects randomized and treated. Of the 59 subjects randomized and treated, 2 subjects were withdrawn after the start of treatment (1 *insulin glulisine*, 1 insulin aspart). The ITT population was defined as all subjects randomized and treated, and consisted of 59 subjects. Subjects were included in the safety analyses if they had both a pretreatment and an on-treatment value available and thus, the number of subjects included in the analyses for each variable varied. The mean age of the population was 45.8 years and 100% were white.

A total of 34 (57.6%) subjects had at least one reported TEAE: 14 (48.3%) *Insulin glulisine* subjects and 20 (66.7%) Insulin aspart (Novolog) subjects. Serious TEAEs were reported in 9 (15.3%) subjects: 5 (17.2%) *insulin glulisine* subjects and 4 (13.3%) Insulin aspart (Novolog) subjects. There was a low and similar monthly rates of catheter occlusion in both treatment arms (*insulin glulisine*: 0.08 occlusions/month; insulin aspart: 0.15 occlusions/month). Catheter occlusions coinciding with unexplained hyperglycemia occurred only once in the trial (in an Insulin aspart (Novolog) treated subject). The mean rate of catheter changes was 14.07 changes/month in the *insulin glulisine* group and 14.83 changes/month in the Insulin aspart (Novolog) group. No differences between groups in the reports of unexplained hyperglycemic

episodes (20.7% of *insulin glulisine* and 40.0% of Insulin aspart (Novolog) subjects) either in the presence or absence of overt pump occlusions.

No imbalances between treatments in the number of subjects with infusion site reactions reported as TEAEs (3 *insulin glulisine*, 4 insulin aspart). No cases of diabetic ketoacidosis were reported in the trial. In addition, no relevant differences between treatment groups were noted in parameters of glycemic control, including insulin dose, GHb, FPG, 7-point BG profiles and hypoglycemic episodes, nor in TEAE reporting.

#### **D. Overall Conclusions on Efficacy**

1. In patients with Type 1 Diabetes, *insulin glulisine* was noninferior to insulin lispro (Homolog) for glycemic control as assessed by changes in GHb. No noteworthy difference existed between treatments in the reporting of all types of symptomatic hypoglycemia. Results from quality of life questionnaires corroborated the finding of a similar perception of hypoglycemia in *insulin glulisine* and insulin lispro (Homolog) treated subjects (Trial 3001).
2. Over the 52-week treatment period, *insulin glulisine* provided similar glycemic control to that of insulin lispro (Homolog) in patients with Type 1 Diabetes. The reductions from baseline in GHb seen during the first 26 weeks were lost with continued treatment. During the 52-week treatment period, no noteworthy difference existed between treatment groups in the frequency or rate of all types of symptomatic hypoglycemia (Trial 3011).
3. In patients with Type 2 Diabetes, *insulin glulisine* was noninferior to regular insulin for the change in GHb from baseline. The efficacy of *insulin glulisine* was observed either when used in combination with OHAs or when immediately premixed with NPH in a syringe prior to injection (Trial 3002).
4. Glycemic control waned during the 26-week extension trial in both treatment groups in Type 2 Diabetes. Over the 52-week treatment period, no consistent noteworthy difference existed between treatment groups in the risk of symptomatic hypoglycemia (Trial 3012).
5. Trial 3005 in Type 2 Diabetes showed that *insulin glulisine* was noninferior to regular insulin for the change in GHb from baseline. The efficacy of *insulin glulisine* was also observed when used in combination with OHAs.
6. Trial 3004 showed that postmeal *insulin glulisine* was noninferior to premeal *insulin glulisine* and to regular insulin in terms of the change in GHb from baseline. Premeal *insulin glulisine* was also noninferior to regular insulin. Statistically significant reductions in GHb were observed from baseline in all three treatment groups. The trial was conducted in patients with Type 1 Diabetes.
7. The results of Trial 3006 support the safe use of *insulin glulisine* in CSII therapy administered via an external pump using the MiniMed and Disetronic pumps with MiniMed and Disetronic catheters. The trial was conducted in patients with Type 1 Diabetes.